IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Robertson et al. Group Art Unit: 1637

Serial No.: **09/750,609** Examiner: Chunduru, S.

Filed: December 28, 2000 Atty Docket No.: 1242/27/2/2

Confirmation No.: 6747

For: GENETIC MUTATION UNDERLYING ORTHOSTATIC INTOLERANCE AND DIAGNOSTIC AND THERAPEUTIC METHODS RELATING THERETO

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DECLARATION PURSUANT TO 37 C.F.R. § 1.131

Commissioner for Patents
Washington, D.C. 20231

Sir:

1. I, Dr. David Robertson, am a co-inventor of the invention disclosed and claimed in the subject above captioned U.S. Patent Application Serial No. 09/750,609.

2. I have had the opportunity to review the Official Action mailed on January 2, 2003 from the U.S. Patent and Trademark Office for the above-referenced U.S. patent application.

3. I have also reviewed the following document cited by the United States Patent and Trademark Office in the Official Action mailed on January 2, 2003: Flattem *et al.* (1999), Identification of a coding mutation in the norepinephrine transporter gene which predisposes a family to Orthostatic Intolerance. *Am J Human Genetics* 65:A43.

4. The invention embodied in claims 1-17 of the subject U.S. patent application was invented prior to the October 1999 publication date of Flattem et al.

5. Attached hereto as **Exhibit A** is a true and accurate copy of an invention disclosure form submitted to the Office of Technology Transfer at Vanderbilt University. Exhibit A predates the October 1999 publication date of Flattem et al.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

David Robertson MD

Dr. David Robertson

2 May 2003

Date

EXHIBIT A

CONFIDENTIAL

Invention Disclosure Form

(Please complete and return to Office of Technology Transfer)

VU9972

VU NUMBER:
(Assigned by the Office of Technology Transfer)

1. **Invention Title:** A Genetic Mutation in the Human Cocaine and Antidepressant-Sensitive Norepinephrine Transporter Underlying Orthostatic Intolerance, a Chronic Fatigue Syndrome

2. **Inventor(s) Information:**

Dr. David Robertson (409-78-0747)
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*Persons who contributed to the conception or reduction to practice of the invention. Inventorship has strict legal meaning under patent law and is finally determined by patent counsel.

**Home address and citizenship are required for a patent application. If the inventor is not a U.S. citizen, please indicate whether or not he/she is a permanent resident of the U.S.

3. **Contract or Grant Number and Funding Sponsor's Name:** (If you received full or partial support during any stage of the research resulting in this invention, or if you have acknowledged or plan to acknowledge a funding source in a publication or grant progress report in which you describe the invention, that funding source must be listed here.)

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4. If there was **non-federal funding**, are there any terms in the funding documents relating to rights in research results (right of first refusal or option)? _X_NO ___YES If yes, attach copy of funding document's requirements. N/A

5. **Was invention made from or does it incorporate materials provided by a third party?** _X_NO ___YES If yes, attach copy of relevant agreement(s).

6. **Earliest conception date and place:** November 24th, 1998 - Date of discovery of transporter mutation in orthostatic intolerant proband.

7. **Invention Description** (draft manuscript or copy of grant proposal may be submitted): (Briefly summarize the nature and function of your invention. State such factors as: general purpose; novel features; advantages and improvements over current technologies; specific utility in the marketplace; and potential commercial interests. Describe the current stage of development of the invention, enclosing any photographs or drawings of a

prototype or conceptual design.) The invention is the discovery of a mutation in the human L-norepinephrine (NE) transporter (NET) gene (SCN2) that alters the encoding sequence of the transporter protein. The mutation has been identified in an individual who is a heterozygote and is carried by other family members and was transmitted from her mother. The coding sequence mutation results in a change of highly conserved alanine residue at amino acid 457 to a proline, a substitution that is known to disrupt the secondary structure of alpha helices common in membrane proteins. The mutation causes the transporter to be nonfunctional and appears to be capable of reducing function of the protein made from a normal gene (dominant negative actions). Individuals who carry a single copy of the mutation have a significantly elevated heart rate upon standing relative to those lacking the mutation, an increased spillover of norepinephrine into the blood and a reduced DHPG/NE ratio upon standing. All family members who report lightheadedness upon prolonged standing or who exhibit tachycardia upon standing carry the mutant allele. The mutation is not a common polymorphism as determined from genetic analyses of more than 200 unrelated individuals. The NET is responsible for removal of NE from synapses in the heart, brain and other sympathetically innervated tissues including blood vessels. The NET is a target for antidepressants and altered NE has been implicated in mental illness, hypertension and heart disease. The discovery of the mutant NET in this family will allow for 1) immediate genotyping of patients with similar diagnoses as the proband, 2) the development of screens for other mutations in the NET gene that may underlie similar disorders, 3) the evaluation of other mutations in homologous or functionally related genes, and 4) the evaluation of NETs as targets for autoimmune antibodies that may contribute to chronic fatigue syndrome.

8. **Prior Disclosures:** (a.) Date of disclosures (oral or written) to other persons--list names of such persons or groups, conferences, society meetings, abstracts/poster presentations, funded grant proposals describing the invention, etc.: (b.) Date and citation (e.g., particular journal) of any publication (including publication over the internet), including abstracts and theses, describing the invention or the technology--attach copies of all such documents published or soon to be published. April 1st, 1999, seminar for Vanderbilt Bench to Bedside Conferences (R. Blakely and D. Robertson); April 13th 1999, seminar to Harvard Dept. Of Neurobiology (R. Blakely); April 15th, 1999 NASA Neurolab Seminar (D. Robertson); and April 28th, 1999, seminar to Patient-Oriented Research Conference (J. Shannon). No publications other than abstracts.

9. **Non-confidential Commercial Statement:** (What does this technology do and what problem does it solve? How is it better than what is already available?) The mutation allows for the first genetic test to be conducted for one form of chronic fatigue or mitral valve prolapse which we describe as orthostatic intolerance or postural tachycardia syndrome (POTS). The technology allows for the development of this test and the development of other tests in the same gene at other loci that may contribute to similar illnesses. The awareness of a phenotype associated with the mutation in the antidepressant-sensitive NET allows for evaluation of the role of the NET gene in mental illness and thus the development of genetic tests for increased susceptibility to mental and autonomic illnesses. This is the first neurotransmitter transporter gene defect that has been shown to be linked to a disorder. The precedent act opens the door for screening for other genetic mutations in genetically related transporters such as the serotonin transporter or dopamine transporter. These latter transporters have been implicated in depression anxiety, pscyhostimulant abuse (cocaine/amphetamine) and attention-deficit disorder. Our work allows for genetic inspection of transporter genes associated with these disorders. Our work may also allow for an examination of whether circulating antibodies

against the NE transporter are contributory to OI or other chronic fatigue disorders.

10. **Companies that may be interested in licensing or spons ring further research:** Merck, Pfizer, Abbott Lilly, GLAXO, McNeill

11. **What do you see as the greatest impediment to the adopti n of your invention for commercial use?** The next steps will be to use the identified mutation to understand other forms of illness. The variability associated with phenotypes and the impact of unknown genetic background issues may render some carriers of these mutations asymptomatic, however this in itself may be important to discover as it may point to modifier genes that could not be understood without prior knowledge of this mutation.

12. **Signature(s):** The inventor(s) must provide a signature and date in the appropriate space(s) given below.

My signature below acknowledges and confirms my agreement to the provisions concerning ownership of technology in the current Vanderbilt Faculty Manual. I agree to cooperate fully with the University in its application of those provisions, including executing whatever assignments of rights or other documents are necessary to allow the University to apply for a patent, license or otherwise develop or commercialize the invention that is the subject of this disclosure. (Final decision as to inventorship will be determined by a patent attorney.)

Inventor(s): Randy Blakely — David Rutter

Date: 5/12/99 — 5/12/99

A witness who understands the invention must also sign and date this Disclosure Form.

Witness: Dorothea L Bremer

Date: 5-12-99